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ZnO Nanoparticles: A Mild and Efficient Reusable Catalyst for the One-Pot Synthesis of 4-Amino-5pyrimidinecarbonitriles Under Aqueous Conditions

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ZnO NANOPARTICLES: A MILD AND EFFICIENT REUSABLE CATALYST FOR THE ONE-POT SYNTHESIS OF 4-AMINO-5-PYRIMIDINECARBONITRILES UNDER AQUEOUS CONDITIONS

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An efficient method for the synthesis of 4-amino-5-pyrimidinecarbonitriles by three-component reaction of malononitrile, aldehydes, and N-unsubstituted amidines, under aqueous conditions, using ZnO nanoparticles as catalyst is reported. The catalyst exhibited remarkable activity and is recyclable.

Keywords: Aldehydes; amidines; 4-amino-5-pyrimidinecarbonitriles; malononitrile; ZnO nanoparticles

INTRODUCTION

Heterocyclic compounds occur widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals that are vital for enhancing the quality of life.^[1]

Pyrimidine is one of the most popular *N*-heteroaromatic compounds incorporated into the structures of many pharmaceuticals. Some such compounds are analgesics,^[2] antihypertensives, antipyretics, and anti-inflammatory drugs.^[3] Pyrimidines occur in some pesticides,^[4] herbicides, and plant growth regulators.^[5]

The organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvents but also because water exhibits unique reactivity and selectivity, different from those obtained in conventional organic solvents. Novel reactivity as well as selectivity that cannot be attained in conventional organic solvents are challenging goals in aqueous chemistry.^[6] The significant enhancement in the rate of reaction has been attributed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding.^[7] Thus, the use of water instead of organic solvents an essential component of sustainable chemistry.^[8]

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Scheme 1. Synthesis of 4-amino-5-pyrimidinecarbonitriles.

ZnO, a wide-band-gap semiconductor with large excitation binding energy, possesses unique properties.^[9,10] The size and morphology of ZnO nanoparticles have great influences on their performances. Because the properties of nanomaterials depend on their size and shape, new synthetic strategies in which the size and shape of nanostructures can be easily tailored are important.^[11]

With the aim to develop more efficient synthetic processes, reduce the number of separate reaction steps, and minimize by-products, and in continuation of our recent interest in the construction of heterocyclic scaffolds,^[12] we herein describe a practical, inexpensive method for the preparation of 2-amino-5-pyrimidinecarbonitriles **4** via multicomponent reactions of aldehydes **1**, malononitrile **2**, and amidines **3** in the presence of ZnO nanoparticles (Scheme 1).

Our catalytic strategy was first evaluated by treating benzaldehyde and malononitrile with guanidinum carbonate in water for 15 min at room temperature using catalytic amounts (10 mol%) of ZnO. This reaction successfully afforded the desired 4-amino-5- pyrimidinecarbonitrile in 93% yield. Without ZnO nanoparticles, the same reaction generated only 25% of 4-amino-5-pyrimidinecarbonitrile over the same period of time.

To investigate the advantageous role of water as a solvent for this method, comparative reactions were carried out in other solvents. The reaction of benzaldehyde, guanidinum carbonate, and malononitrile was carried out in CHCl₃ and CH₂Cl₂ under similar reaction conditions where it furnished the 2,4-diamino-6-phenyl-5pyrimidinecarbonitrile **4b** in yields of only 48 and 53%, respectively. When the same reaction was carried out in more polar solvents such as tetrahydrofuran (THF), MeCN, and EtOH under identical conditions, **4b** was obtained in yields of 68, 73, and 78%, respectively (Table 1). It is remarkable that the reaction carried out in water afforded

	2	19	
Entry	Solvent	Time (min)	Yield (%)
1	CH ₂ Cl ₂	60	53
2	THF	30	68
3	CHCl ₃	60	48
4	EtOH	30	78
5	MeCN	30	73
6	H ₂ O	15	93

Table 1. Solvent effect for synthesis of 4-amino-5-pyrimidinecarbonitrile^a

^{*a*}Reaction conditions: benzaldehyde **1** (1 mmol), malononitrile **2** (1 mmol), guanidinum carbonate **3** (1 mmol), and ZnO nanoparticles (10 mol%), H₂O, room temperature.

Entry	Catalyst	Time (min)	Amount of catalyst (mmol)	Yield (%)
1	ZnO nanoparticle	15	(0.1 mmol)	93
2	Bulk ZnO	30	(0.5 mmol)	73
3	Basic Al_2O_3	15	(0.3 mmol)	85
4	Al_2O_3	30	(0.5 mmol)	78

Table 2. Comparison between ZnO nanoparticles, bulk ZnO, Al_2O_3 , and basic Al_2O_3 catalysts in the reaction of benzaldehyde, malononitrile, and guanidinum carbonate^{*a*}

^{*a*}Reaction conditions: benzaldehyde **1** (1 mmol), malononitrile **2** (1 mmol), guanidinum carbonate **3** (1 mmol), and ZnO nanoparticles (10 mol%), H_2O , room temperature.

2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile **4b** in excellent yield (93%), which is significantly more than those obtained for the volatile/toxic/polar organic solvents.

The role of water as the reaction medium and its mechanism are still not clear. Recently, it has been reported that some organic molecules can react on the surface of water. Often a very strong enhancement of reaction rates was noticed in this case, particularly when at least one component involved in this reaction bore a polar group, enabling some degree of solubility. The significant enhancement in the rate of reaction has been attributed to hydrophobic packing, solvent polarity, hydration, and hydrogen bonding.^[13]

The ZnO nanoparticle catalyst was studied along with other known solid base catalysts using the reaction of benzaldehyde, malononitrile, and guanidinum carbonate in 5 mL of water as a model system for the synthesis of the corresponding 4-amino-5-pyrimidinecarbonitrile. The results are summarized in Table 2. The results show that the three-component reactions catalyzed by basic Al_2O_3 and Al_2O_3 proceed over longer reaction times and afford moderate product yields. The size of ZnO plays an important role in terms of yields and reaction times. Changing the size of the particles from nanoparticles to bulk resulted in a drop in the catalytic activity. It is interesting to note that the ZnO nanoparticle catalyst catalyzes the present reaction in excellent yield within a shorter reaction time than the other solid base catalysts. It appears that the basicity of the catalyst plays a prominent role.

The generality of this process was demonstrated by the wide range of substituted aldehydes and *N*-unsubstituted amidines to synthesize the corresponding products in good to excellent yields (Table 3). The results in Table 3 indicate that

		•		
Entry	R	R′	Yield (%)	Mp (°C) Observed (lit.) ^[13]
a	C ₆ H ₅	Ph	98	212 (212)
b	C_6H_5	NH_2	93	230 (228–230)
с	$4-MeC_6H_4$	Ph	91	208–210 (210)
d	4-MeC ₆ H ₄	NH_2	96	130 (130)
e	4-ClC ₆ H ₄	Ph	93	221-222 (222)
f	$4-ClC_6H_4$	$\rm NH_2$	98	231 (229–231)

Table 3. Synthesis of 4-amino-5-pyrimidinecarbonitriles^a

^{*a*}Reaction conditions: benzaldehyde 1 (1 mmol), malononitrile 2 (1 mmol), *N*-unsubstituted amidines 3 (1 mmol), and ZnO nanoparticles (10 mol%), H_2O , room temperature, 15 min.



Scheme 2. Plausible reaction mechanism.

the aromatic aldehydes bearing different functional groups such as chloro, nitro, methyl, or methoxy groups were able to undergo the condensation reaction.

A mechanism for the reaction is outlined in Scheme 2. The reaction occurs via initial formation of the cyano olefin 3 from the condensation of aryl aldehyde 1 and malononitrile 2. The second step is followed by Michael addition, cycloaddition, isomerization, and aromatization to afford the 4-amino-5-pyrimidinecarbonitriles 5. Intermediate 4 is not stable and is easily oxidized by air to produce compound 5.

The insolubility of the catalyst ZnO in different organic solvents and water provided an easy method for its separation from the product. Recycling experiments were performed using the ZnO nanoparticle catalyst for the synthesis of 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile **4b**. These recycling experiments show that the ZnO nanoparticle catalyst catalyzes the reaction with consistent activity even after four cycles. Infrared (IR) spectra of the resulting solids indicate that the catalyst can be recovered without structural degradation (Fig. 1).



Figure 1. IR spectrum of nanosized ZnO before (a) and after (b) use.

Entry	Method	Catalyst	Solvent	Time (min)	Yield (%)
1	Microwave-assisted conditions ^[13]	Sodium acetate	Solvent-free	5	70
2	Microwave-assisted conditions ^[13]	Without a catalyst	Solvent-free	10	52
3	Microwave-assisted conditions ^[13]	Sodium acetate	Toluene	1.5	74
4	Microwave-assisted conditions ^[13]	Triethylamine	Toluene	0.5	90
5	Microwave-assisted conditions ^[13]	Sodium acetate	Water	0.5	73
6	Reflux ^[13]	Sodium acetate	Water/ethanol (1:1)	360	78
7	Stirrer at room temperature	ZnO nanoparticles	Water	15	93

Table 4. Synthesis of 4b under different reaction conditions

Note. All reactions were carried out at 300 W of microwave irradiation.

Finally, the efficacy of the present method for the synthesis of **4b** was compared with other reported procedures (Table 4).^[13] It revealed that ZnO nanoparticle is an efficient, environmentally benign catalyst in the synthesis of 2,4-diamino-6-phenyl-5-pyrimidinecarbonitrile.

In conclusion, we have reported here in several noteworthy features of a new catalyst for the synthesis of 4-amino-5-pyrimidinecarbonitriles through the three-component reaction of malononitrile, aldehydes, and *N*-unsubstituted amidines using ZnO nanoparticles. This protocol offers many attractive features such as reduced reaction times, greater yields, and economic viability of the catalyst. The reaction proceeds under aqueous conditions. Isolation of the catalyst is easily achieved, and the catalyst is recoverable and can be used in several runs without loss of catalytic activity. This makes the method economic, benign, simple, and convenient for the synthesis of 4-amino-5-pyrimidinecarbonitriles.

EXPERIMENTAL

Preparation of Zno Nanoparticles

Zinc nitrate (4.05 g) was added to a beaker containing 28 ml saturated NH₄HCO₃ solution, and 14 ml ammonia (28 wt%) was gradually dropped into the beaker under magnetic stirring at room temperature. The reaction was run until zinc nitrate was dissolved completely, and the obtained solution was then added into four times its volume of distilled water. The reaction was carried out under magnetic stirring at 60 °C for 1 h. The precursor was separated by centrifugation, dried at 60 °C for 12 h, and finally calcined at 450 °C for 3 h in ambient oxygen. The morphology and size distribution of ZnO nanoparticles were determined by scanning electron micrography (SEM) (Fig. 2).



Figure 2. Scanning electron micrograph of nanosized ZnO particles.

General Procedure for the Preparation of 4-Amino-5pyrimidinecarbonitriles

A mixture of aldehyde 1 (1 mmol), malononitrile 2 (1 mmol), amidine hydrochloride or guanidinum carbonate (1 mmol), and ZnO nanoparticles (0.1 mmol) in H2O (5 mL) was stirred for 15 min [the progress of the reaction was monitored by thin-layer chromatography (TLC) using *n*-hexane/ethyl acetate as an eluent (2:3)]. Upon completion of the reaction, the reaction mixture was filtered to isolate the solid product. Then the solid product was diluted with chloroform, and the catalyst was removed by simple centrifugation (the catalyst is not soluble in chloroform). After evaporation of solvent, more purification was obtained by recrystallization from ethanol.

Spectral data of 4-amino-5-pyrimidinecarbonitriles described in this article are the same as those reported in a previously published paper.^[14]

Reusing the Catalyst

After completing the model reaction, the catalyst was separated by centrifugation, washed three times with 10 ml of chloroform, dried at $120 \,^{\circ}$ C for 1 h, and subjected to a second run of the reaction.

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